CASE REPORT

Acute profound thrombocytopenia following angioplasty: the dilemma in the management and a review of the literature

S N Makoni

Abstract

Abciximab, heparin, and clopidogrel are often used together in the setting of coronary syndromes. These drugs are associated with thrombocytopenia and it is important to quickly discriminate the cause of this complication as it has implications for the management of thrombocytopenia and the coronary syndrome. This case highlights some of the dilemmas that may arise as no test can definitively identify the offending drug, and stopping these drugs can affect the outcome of the coronary event including stent thrombosis.

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Keywords: profound thrombocytopenia; abciximab; heparin; clopidogrel

Abciximab, a platelet glycoprotein IIb/IIIa inhibitor that blocks the final common pathway of platelet aggregation, thereby exerting a potent antiplatelet effect, is used in the treatment of patients undergoing percutaneous coronary intervention.[1] In the EPIC (evaluation of IIb/IIIa platelet receptor antagonist 7E3 in preventing ischemic complications) study there was a significant improvement in 30 day and six month clinical outcomes when abciximab was used in percutaneous coronary intervention compared with patients who had not received abciximab. This benefit, however, comes with potential complications of bleeding and thrombocytopenia. The EPILOG (evaluation in PTCA to improve long term outcome with abciximab GP IIb/IIIa blockade) trial showed that abciximab administered with low dose weight adjusted heparin diminished the risk of ischaemic complications within 30 days by 56% among patients undergoing percutaneous transluminal coronary angioplasty (PTCA) without increasing bleeding complications.[2] Pooled data from three placebo controlled, randomised trials (EPIC, EPILOG, and EPISTENT (evaluation of platelet IIb/IIIa inhibitor for stenting)) of abciximab treatment during percutaneous coronary intervention identified 178 patients (2.4% of 7290 patients) in whom thrombocytopenia developed after enrolment. Mild, severe, and profound thrombocytopenia were defined as platelet counts < 100 000, < 50 000, and < 20 000/mm^3, respectively. Among patients with thrombocytopenia, the incidence of profound thrombocytopenia was 8.5%.[3] Clopidogrel is a thienopyridine derivative that irreversibly inhibits platelet aggregation by selectively binding adenylate cyclase coupled ADP receptors on the platelet surface. It has superior efficacy over aspirin in terms of prevention of myocardial infarction and vascular death.[4]

Case report

A 68 year old black man with a history of right coronary artery stent one year before presentation was admitted after a positive exercise stress test. His medications were atorvastatin, metoprolol, aspirin, clopidogrel, and amlodipine. Examination showed a normal blood pressure, weight of 95 kg and no signs of heart failure or organomegaly. Haemoglobin was 13.9 g/dl, platelets 174 000, and coagulation profiles were normal. Cardiac catheterisation showed 99% stenosis of the stent. He had balloon dilatation and stent replacement. During the procedure he received heparin and abciximab infusions. After the procedure clopidogrel, aspirin, and abciximab were continued. Seven hours after initiation of abciximab, the platelet count was 5000. Abciximab was stopped and complete blood count rechecked. A peripheral smear confirmed thrombocytopenia without platelet clumping or schistocytosis. The patient was noted to have mild haematuria and was transfused with 12 units of pooled platelets. On days 2 and 3 platelet counts were 124 000 and 53 000, respectively. Mild haematoma was noted at the site of a needle stick. Prothrombin time was 11.4 seconds, partial thromboplastin time 22.7 seconds, FDP 8, fibrinogen 549, and blood cultures were negative. A serotonin release assay and enzyme linked immunosorbent assay (ELISA) for heparin dependent antiplatelet factor 4 antibody were sent to a reference laboratory to exclude the possibility of heparin induced thrombocytopenia (HIT) type II. On day 4 the platelet count was 40 000 and the patient was started on danaparoid, while HIT assay results were pending. On day 5 the platelet count was 45 000/mm^3 and HIT assays were negative. Danaparoid was stopped,

Department of Internal Medicine, Mercy Fitzgerald Hospital, 1500 Lansdowne Avenue, Darby, Pennsylvania 19023, USA
S N Makoni

Correspondence to:
Dr Makoni
sncmakoni@hotmail.com

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no further drop in platelet count was noted, and the patient was discharged.

Discussion

It is important to distinguish pseudothrombocytopenia from true thrombocytopenia related to abciximab, HIT, clopidogrel induced thrombotic thrombocytopenic purpura (TTP), and other causes because pseudothrombocytopenia involves no increased thrombotic or haemorrhagic risk and has no clinical significance. Pseudothrombocytopenia is caused by EDTA dependent clumping of platelets in vitro. When the complete blood count is repeated using blood collected into citrate or heparin, pseudothrombocytopenia is corrected. The incidence of pseudothrombocytopenia in the general population was 0.1% compared with 1.1% in patients on abciximab in the EPIC trial.[5] Pseudothrombocytopenia in the present patient was excluded by absence of platelet clumping on peripheral smear.

There is a significant increase in thrombocytopenia when abciximab and heparin are used compared with placebo and heparin.[6] A recent observation that incidence and severity of thrombocytopenia may be reduced by the concomitant administration of low molecular weight heparin (enoxaparin) instead of unfractionated heparin also suggests a possible interaction between abciximab and the type of heparin.[6] Thrombocytopenia related to abciximab is frequently evident within the first 2–4 hours, occurs rapidly, and may be reversed by platelet transfusion. Recovery starts after treatment is stopped and occurs at 20 000/mm^3 platelets per day, which reflects normal bone marrow response. In one analysis thrombocytopenia associated with abciximab treatment for PTCA was more frequent in patients who were older (> 65 years) had a lighter weight (< 90 kg), and had a lower baseline platelet count (< 200 000),[7] as was the case in this patient.

There are at least two discrete forms of HIT. The most clinically important is type II, a disorder of delayed onset but persistent thrombocytopenia that begins 4–10 days after exposure to heparin and may be associated with venous and arterial thromboses. Rarely are precipitous drops in platelet counts observed within 24 hours unless the patient has received heparin within the previous two months.[7] Type II is caused by IgG antibodies specific for a complex of heparin and platelet factor 4. Binding of these antibodies to circulating platelets leads to activation, aggregation, and fragmentation of platelets, to thrombocytopenia, and, if the thrombocytopenia is untreated, to arterial and venous thromboses (white clot syndrome) caused by the procoagulant effect of platelet microparticles. Testing for the presence of heparin dependent antibodies to diagnose HIT is time consuming and not completely reliable.[7] When heparin is stopped in suspected HIT, another anticoagulant is required to prevent life threatening thromboembolic complications including skin necrosis, gangrene of the extremities, myocardial infarction, pulmonary embolism, and stroke. In the present case danaparoid sodium was used. Enoxaparin may cross react with heparin antibodies causing thrombosis and therefore is contraindicated.

Clopidogrel may induce TTP, a disorder characterised by diffuse microvascular occlusion of arterioles and capillaries resulting in ischaemic dysfunction of multiple organs. If TTP is untreated, the mortality rate exceeds 90% and therefore constitutes a medical emergency. Haemolytic uraemic syndrome, a variant of TTP, has been reported in a patient treated with clopidogrel.[8] The absence of fragmented red blood cells and reticulocytes on peripheral smear and a normal renal function made this unlikely. Normal haptoglobin, lactate dehydrogenase, and bilirubin were used to exclude a microangiopathic process. In this patient, other potential causes of thrombocytopenia such as immune thrombocytopenia, and rheumatological and bone marrow disorders were eliminated by a normal baseline platelet count, absence of splenomegaly, and normal prothrombin time, partial thromboplastin time, and FDP, and negative blood cultures.

Thus, profound thrombocytopenia secondary to abciximab and heparin was diagnosed in this patient by exclusion of other causes and the patient was safely managed with platelet transfusion. While the incidence of thrombocytopenia has been observed to increase when abciximab and unfractionated heparin are used together, it is not clear whether clopidogrel used in combination with abciximab and heparin increases the incidence of thrombocytopenia. Future trials should evaluate this.

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